CASK mutation identified by whole exome sequencing in a patient that expands the clinical spectrum for MICPCH syndrome

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Background:

A 23-year-old mixed-European female with no family history of intellectual disability presented with multiple malformations and developmental delays. She exhibits microcephaly, severe intellectual disability, dyspraxia, congenital quadriplegia, dystonia of the upper extremities, spasticity, and scoliosis. Brain imaging revealed pontine and cerebellar hypoplasia with intact corpus callosum. We noted down-slanting palpebral fissures, midface hypoplasia, high-arched palate, dental crowding, large tongue, and long narrow asymmetric face. Chromosome analysis, metabolic testing, and microarray all revealed no abnormalities. Whole exome sequencing revealed c.2065A>T, a single nucleotide change in the *CASK* gene, which is located on chromosome Xp11.4 and encodes for a calcium/calmodulin-dependent serine protein kinase. This protein is essential in synaptic function and brain development. The *de novo* nonsense mutation truncates the CASK protein, which is likely the etiology of the patient's adverse phenotype. The major features in our patient resemble those reported in MICPCH syndrome (microcephaly with pontine and cerebellar hypoplasia). Since MICPCH syndrome is a rare X-lined dominant disorder (OMIM #300749) associated with mutations in the *CASK* gene, we believe our patient expands the phenotypic profile of *CASK* mutations.

Presentations	LMD	Moog	Burglen	Patient	%
Microcephaly	+	25/25	13/13	+	100
Pontocerebellar hypoplasia	+	25/25	13/13	+	100
Normal Corpus Callosum	+	22/22	13/13	+	100
Intellectual Disability	+	23/25	13/13	+	95
Seuzures/abnormal EEG	+	8/25	4/13	+	33
Long philtrum	+	5/23	+*	+	25
Epicanthic folds	+	4/23	+*	+	21
Large Ear	+	12/23	+*	+	54
Prominent nasal bridge	+	14/23	+*	+	63
Axial Hypotonia	+	14/20	+*	-	67
Spasticity	+	10/22	9/11	-	56
Ophthalmologic anomalies†	+	19/24	10/13	+	79
Sensorineural deafness	-	8/23	3/11	+	38
Scoliosis	+	-	5/11	+	50
Sleep Abnormalities◊	-	-	8/11	+	75
Long Taper Fingers	-	-	3/13	+	29
Dystonia	-	-	9/11	+	83
Macroglossia	-	-	-	+	0
Contracture of large joints	-	-	-	+	0
Laxity of small joints	-	-	-	+	0
Dental crowding	-	-	-	+	0

*Feature is "present" but the exact number of patients with it is unspecified, and it will not be a part of the percentage calculation.
†Ophthalmologic anomalies vary greatly (e.g. optic dysplasia, nystagmus, hyperopia); our patient has hyperopia.
◊Burglen, *et al.* report primary insomnia and interruptions, while our patient has hypersomnolence.

Reference:

1) Najm J, *et al.* Mutations of CASK cause an X-linked brain malformation phenotype with mirocephaly and hypoplasia of the brainstem and cerebellum. *Nat Genet* 2008;40:1065-7
2) Moog U, *et al.* Phenotypic spectrum associated with CASK loss-of-function mutations. J Med Genet 2011;48:741-51
3) Hayashi S, *et al.* The CASK gene harbored in a deletion detected by array-CGH as a potential candidate for a gene causative of X-linked dominant mental retardation. Am J Med Genet A 2008; 146A:2145-51
4) Hackett A, *et al.* CASK mutations are frequent in males and cause X-linked nystagmus and variable XLMR phenotypes. *Eur J Hum Genet* 2010;18:544-52
5) Burglen L, *et al.* Spectrum of pontocerebellar hypoplasia in 13 girls and boys with CASK mutations: Confirmation of a recognizable phenotype and first description of a male mosaic patient. Orphanet J Rare Dis 2012;7:18.

Method:

Genomic deoxyribonucleic acid (gDNA) was isolated from the whole blood of the patient and both parents. Informed consent was obtained from all family members involved in the testing process. Samples were prepared using the SeqCap EZ VCRome 2.0 (Roche NimbleGen, Madison, WI). The enriched exome libraries were sequenced using paired-end, 100-cycle chemistry on the Illumina HiSeq 2500 (Illumina, San Diego, CA). Data analysis and medical interpretation were performed as previously described (Farwell, 2014).

Complete Exome Results

Gene	Alteration	Proband	Father	Mother	Conclusion
CASK	c.2065A>T (p.K689)	Heterozygous	Negative	Negative	De novo
CDH15	c.1017dupA (p.V340Sfs*6)	Heterozygous	Positive	Negative	Inherited
PIGV	c.781DUPA (p.T261NFS*14)	Heterozygous	Positive	Negative	Inherited

- ✧ *CDH15* mediates cell-cell adhesion and alteration of the gene clinically correlates to intellectual disability. It maps to chromosome 16q24.3
- ✧ Mutation of *PIGV* clinically correlate to hyperphosphatasia with intellectual disability; the gene maps to 1p36.11
- ✧ One publication reporting four *CDH15* mutation to be autosomal dominant, but our patient's father displays no intellectual disability. Our patient's phenotypic spectrum is also inconsistent with the clinical association with *CDH15* mutation.
- ✧ The *PIGV* mutations is non-contributory to the patient's adverse phenotype due to recessive inheritance.

Conclusion

- ✧ Whole exome sequencing identified a nonsense mutation within the *CASK* gene.
- ✧ Our patient exhibits not only the cardinal features for MICPCH syndrome (Moog 2011; Burglen 2012) but also adds other features (joint laxity, dental crowding, macroglossia, and contracture of large joints), expanding the phenotypic spectrum of MICPCH.
- ✧ Being one of the oldest living patient diagnosed with *CASK* mutation, our patient can further elucidate the MICPCH syndrome's progression and illuminate on the prognosis.